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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,612	02/24/2004	Yuping Qiu	QA0283 NP	2956

23914 7590 01/22/2007

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EXAMINER	
LEESER, ERICH A	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,612	QIU ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election of Group I in the reply filed on November 30, 2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Group I, that being claims 1-16, are drawn to various pyrazolopurine-based tricyclic compounds and compositions, classified in classes 544 and 514, subclasses 251 and 267 respectively, are currently pending. Non-elected claims 17-19 are withdrawn form consideration.

The restriction requirement is made FINAL.

Priority

Examiner acknowledges that this application claims the benefit of domestic priority of provisional application 60/449,770 filed on February 25, 2003.

Information Disclosure Statement

The IDS, filed on November 3, 2004, is made of record.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making "solvates" of the

claimed invention. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

1. The nature of the invention:

The invention is drawn to the compounds of formula (I), and enantiomers, diastereomers, salts and solvates thereof. The specification is not adequately enabled to show how to make solvates of the compounds of formula (I).

The compounds of formula (I) embrace pyrazolopurine-based tricyclic compounds substituted with variable groups R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{7a}, R^{7b}, R^8, R^{8a}, R^{8b}, R^{8c}, R^9, R^{9a}, R^{9b}, R^{9c}, R^{10}, R^{10a}, R^{10b}, R^{11}, R^{12}, R^{12a}, R^{13}, R^{14}, U^1, U^2, U^3, U^4, V^{1a}, Y^1, Y^2, Y^3, Y^4, Y^5, Y^6, Y^a, Y^b, Y^c, Y^d, Z^1, Z^2, Z^3, Z^{1a}, Z^{2a}, Z^{3a}, Z^{1b}, Z^{2b}, Z^{3b}, Z^{1c}, Z^{2c}, Z^{3c}, Z^{1d}, Z^{2d}, Z^{3d}, Z^{1e}, Z^{2e}, Z^{3e}, $Z^{1\text{-}1e}$, $Z^{2\text{-}2e}$, $Z^{3\text{-}3e}$ and t.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) would result in at least hundreds of thousands of compounds. Thus, the genus embraced in claim 1 is quite large and there is no teaching of any solvate of any compound out of this large genus.

2. The state of the prior art:

A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

3. The predictability or lack thereof in the art:

For the reasons stated *supra*, the solvates as applied to the above-mentioned compounds claimed by the Applicant are not art-recognized compounds and hence there should be an enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvates of the instant compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that

the instant compounds formed solvates. Hence it is clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance.

5. The presence or absence of working examples:

There is no working example of any solvate formed. These cannot be simply willed into existence. "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that solvates of these compounds exist and therefore can be made.

6. The breadth of the claims:

The breadth of the claims include all of the hundreds of thousands of compounds of formula (I) of claim 1 as well as the presently unknown list of potential solvate derivatives embraced by the word "solvates." The term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the

specification. It would not be obvious to one skilled in the art how to make the solvates of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

7. The quantity of experimentation needed

The specification has no support, as noted *supra*, for the desired solvates of the compound of formula (I). As noted above, the genus embraces hundreds of thousands of compounds and hence the breadth of the claims is broad. The quantity of experimentation needed would be an undue burden on one skilled in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated *supra*. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvates of the compound of formula (I) embraced in the instant claims.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making a "prodrug" of the claimed compounds. The claim contain subject matter that is not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to make and use the invention.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack

thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

1. The nature of the invention

A pharmaceutical composition comprising at least one compound of formula (1), or a pharmaceutically acceptable salt, hydrate or prodrug thereof...

2. The state of the prior art:

The state of the prodrug art is summarized by Wolff, Manfred E., *Burger's Medicinal Chemistry and Drug Discovery*, Fifth Ed., Vol. 1: Principles and Practice, John Wiley & Sons, 1995, 975. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker, Gilbert S. et al., *Modem Pharmaceutics*, Marcel Dekker, New York, 1996, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

3. The predictability or lack thereof in the art:

It is well-established that "the scope of enablement varies inversely to the degree of unpredictability of the factors involved", "and physiological activity is generally considered to be an unpredictable factor." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Finding a prodrug is an empirical exercise. Predicting if a certain

ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate, is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. First, the prodrug must itself be biologically inactive. Second, the prodrug must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

4. The amount of direction or guidance present:

The amount of guidance or direction refers to that information in the application that teaches exactly how to make or use the invention. The specification contains no working examples of a prodrug of a compound of the formula (I). Thus, undue experimentation will be required by one skilled in the art to make a prodrug of the claimed invention.

5. The presence or absence of working examples:

The specification contains no working examples of a prodrug of a compound of the formula (I). Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

6. The breadth of the claims:

The breadth of the claims includes all of the hundreds of thousands of compounds of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by the word "prodrug." The term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification.

Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make a claimed prodrug of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make a prodrug of the present invention. Therefore, the scope of enablement provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

7. The quantity of experimentation needed

Substantial and undue experimentation would be needed to practice Applicant's invention because he did not sufficiently detail how to make and use a "prodrug." MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to make and use the instantly claimed invention.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected if it is dependent on a rejected claim and shares the same indefiniteness.

Recitation of "prodrug" in claim 16 renders the claim indefinite. Prodrugs, in general, are compounds, which undergo *in vivo* hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, it is not clear what the difference is between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered a prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon *in vivo* transformation, then the compound bearing the variable group would be deemed as inactive, which is not what the claim recites.

Furthermore, the issue of the second paragraph of 35 U.S.C § 112 is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrug" are molecules whose structure lie outside the subject matter, but upon metabolism in the body are converted to active compounds falling within the structural scope. The claim describes the function intended but provides no specific structural guidance as to what constitutes a "prodrug." Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 16. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

Claims 6, 8 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The following apply. Any claim not specifically rejected is rejected if it is dependent on a rejected claim and shares the same indefiniteness.

These claims are rejected due to minor clerical errors which are currently causing ambiguity and therefore, indefiniteness. Claim 6 includes the word "of" twice in succession. One of them needs to be deleted. The issue with claims 8 and 12 has to do with the location of the bond of the stated variable groups. Line 2 on page 132 and lines 9 and 17 on page 133 have "U^{4-}" where it is believed that "U^{4}-" was intended. Clarification is suggested.

Claim Rejections 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ikesu et al., U.S. 5,306,610.

Claims 1-7 are drawn to compounds of formulas (I) which embrace pyrazolopurine-based tricyclic compounds substituted with variable groups. Claims 8-11 are drawn to compounds of formula IIa with a more narrowly defined R^6. Claims 12-15 are drawn to compounds of formula IIb with Z^{1d} in the para position instead of the meta position of formula IIa. Claim 16 is drawn to a pharmaceutical composition comprising a compound of claim 1.

Ikesu et al. teaches photographic couplers comprising compounds which have the same core structure of the elected claims. Applicant's attention is directed to the last two chemical cores disclosed in column 5 because column 3, beginning at line 41 provides the definition of R^2: "The substituent represented by R^2 is not particularly limited so long as it is a group which can substitute nitrogen atom, but may representatively include ... heterocyclic ring." Note where R^3 and R^4 of the instant invention combine to form a heterocyclic ring. The core and species that can be prepared as taught by the reference render claims 1-5 and 16 obvious. Pharmaceutical compositions of the compounds of the prior art, which use the pharmaceutically acceptable carrier water and render the instant compounds obvious can be found at steps (2) and (3) in columns 13 and 14, respectively. Pharmaceutical compositions of the compounds of the prior art render the instant compounds obvious because Applicant discloses that the invention's compounds are suitable for pharmaceutically acceptable compositions.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to obtain compounds which contain overlapping core structures

as disclosed *supra*. The prior art also discloses the incorporation of these compounds into compositions. The motivation to make compounds according to Ikesu et al. wherein the substituent corresponding to $-NR^3R^4$ in compounds of the present invention is a heterocyclic ring would be to produce photographic couplers because a motivation different than an applicant's motivation is permissible pursuant to MPEP 2143.03.

Allowable Subject Matter

If "solvates" and "prodrug" are deleted in all occurrences, and the $-NR^3R^4$ equal to heterocycle is deleted, then the claims will be in allowable form.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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